REMARKS

Reconsideration and allowance are requested. The claim amendments do not add new matter. They are directed to conforming ordering of the process steps and the punctuation; they are not made for reasons related to patentability. Therefore, they do not change the scope of the claims.

Applicants thank the Examiner for withdrawal of the 35 U.S.C. 112, second paragraph and 35 U.S.C. 112, first paragraph, scope of enablement rejections.

Claims 3-4, 17, 57-63 and 65-66 were examined on the merits. Claims 5-8, 10, 15, 35-47 and 64 were withdrawn from consideration, but their rejoinder is requested. In particular, Applicants request rejoinder of claims 5-8 and 64, all of which are directed to methods of making the conjugates of currently pending claims. The method claims are directed to products of the same scope as the elected product claims.

1. Isolated conjugates of claims 3-4, 17, 57-63 and 65-66 have substantial, specific and credible utility.

Ubiquitilated proteins are degraded in the cell by a proteasome-mediated degradation pathway. The importance of proteasomal degradation is well established in the arts of biochemistry, and cell and molecular biology. In fact, the central role of ubiquitylated proteins in proteolytic pathways was acknowledged in the award of the 2004 Nobel Prize in Chemistry to Aaron Ciechanover, Avram Hershko, and Irwin Rose.

A google search for "proteasomal degradation" returns 498,000 results. A search of PubMed for "proteasomal degradation" returns 2,251 results.

Applicants' invention provides a collection of ubiquitin conjugates of proteins that have been linked to disease states. Thus, a person of ordinary skill in the art will readily recognize the utility of the invention in providing substrates, markers, and controls for studying the ubiquitylation and proteasomal degradation pathways as they relate to the diseases identified in pages 6-22 of the specification.

The claimed conjugates are biomarkers of clinically-relevant ubiquitilation activity. The isolation of the conjugates from biological samples provides a material that is useful for quantifying ubiquitylation activity. The claimed conjugates are also useful substrates

that can be used in assays for quantifying the breakdown of ubiquitylated proteins mediated by the proteosome. In addition, the claimed conjugates are useful substrates for monitoring the ubiquitilation editing activities of ubiquitilation enzymes. Because of their usefulness in measuring these biological activities, the claimed materials are also useful for analyzing the effectiveness of drugs or other therapies against such activities. The claimed conjugates will also have use as controls (e.g., as solutions of known concentration sold in small vials) for assays and other studies of the above-mentioned biological activities.

2. Claims 3-4, 17, 57-63 and 65-66 are adequately supported by the disclosure in Applicants' specification.

Applicants urge that the utility of claimed ubiquitin conjugates is readily apparent to one of ordinary skill in the art.

A patent does not teach, and preferably omits, what is well known in the art. *In re Buchner*, 18 U.S.P.Q.2d 1331, 1332 (Fed. Cir. 1991); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986); *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 221 U.S.P.Q. 481, 489 (Fed. Cir. 1984). Thus, well-established utilities that are known in the art (see citations of the scientific literature on pages 6-22 of the specification) are not required to be explicitly disclosed by Applicants. Withdrawal of this rejection is requested.

3. Claims 3, 17 and 57 are clear and definite.

Applicants urge that the term "polypeptide" is not indefinite within the context of the claims. This term clarifies only the "fragments and derivatives" limitation of the claimed proteins and not the proteins themselves. It is clearly described that claimed polypeptides are "said fragments and derivatives thereof comprise polypeptides of at least 50 amino acids having at least 90% sequence identity to sequences within their corresponding proteins" (see claim 3, emphasis added). Thus, one of ordinary skill in the art will readily determine if the polypeptide falls within the scope of the currently pending claims by aligning the sequence of the polypeptide with the sequences of

claimed proteins, e.g., aprataxin, SLP, HMG17, PinX1, CIR, HMGN3, HSPC144, Cullin 3, CDC6 and tau (see claims 3 and 57). Withdrawal of this rejection is requested.

But if this rejection is not overcome by the above response and the Examiner finds it desirable, Applicants offer in the alternative to amend the claims as follows:

> wherein said fragments and derivatives thereof comprise an amino acid sequence ~~polypeptides~~ of at least 50 amino acids having at least 90% sequence identity to sequences within their corresponding proteins, . . . said conjugate is formed via N-end rule ubiquitylation of an amino acid sequence ~~a polypeptide~~ comprising a destabilizing N-terminal residue and an internal Lys residue

Favorable reconsideration and prompt issuance of the Notice of Allowance is earnestly solicited.

Respectfully submitted,

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